2. (Twice Amended) A compound as claimed in claim 1, wherein the compound further comprises covalently bonded carbohydrates.

3. (Twice Amended) A compound as claimed in claim 1, wherein [the] at least one antigen binding region comprises a variable domain of a heavy antibody chain and a variable domain of a light antibody chain (sFv fragment).

29. (Twice Amended) A compound as claimed in claim 10, which [undergoes] has undergone secretory expression in *Hansenula polymorpha*.

30. (Amended) A compound as claimed in claim 1, wherein [the] at least one antigen binding region and at least one prodrug-activating enzyme form an sFv-β-lactamase fusion protein.

REMARKS

I. Status of Application

Claims 1-33 are pending, with claims 14-22 being withdrawn from consideration. In the Office Action dated August 7, 2000, the Examiner withdrew the previous objection to the specification and the previous rejections under 35 U.S.C. §101 and §112, as well as the previous obviousness-type double patenting rejection. However, the Examiner maintained the objection under 37 C.F.R. §1.75(c) and rejection under 35 U.S.C. §112, second paragraph, of claim 2; the rejection of claims 3 and 30 under 35 U.S.C. §112, second paragraph; and the prior art rejections of claims 1-13 and 25-33 under 35 U.S.C.

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§103(a). Additionally, the Examiner imposed a new rejection of claim 30 under 35 U.S.C. §112, first paragraph. In an Advisory Action dated December 4, 2000, the Examiner denied entry of a previously proposed After Final Amendment dated November 7, 2000, because the proposed amendment "raise[d] the issue of new matter."

By this amendment, Applicants propose to amend claims 1-3 and 29-30, thus placing them in condition for allowance. Support for these amendments may be found in the specification and claims as originally filed. In particular, the amendments of claims 1, 3, and 30 are supported by the specification on page 2, last paragraph. The amendments of claims 2 and 29 are supported by the claims as originally filed. Reconsideration of claims 1-13 and 25-33 is respectfully requested in view of these amendments and in light of the following comments.

II. Objection under 37 C.F.R. §1.75(c) and Rejection under 35 U.S.C. §112 of Claim 2

The Examiner objected to claim 2 under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of independent claim 1. The Examiner's position is that claim 2's recitation of carbohydrates fails to further limit the protein of independent claim 1. The Examiner further rejected claim 2, along with claims dependent thereon, under the second paragraph of 35 U.S.C. §112, as allegedly confusing as to what is meant by the phrase "comprises covalently bonded carbohydrates."

The Examiner suggests that the word --further-- be inserted before "comprises" in claim 2 in order to overcome the objection and rejection of these claims. Applicants

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have amended claim 2 in accordance with the Examiner's suggestion. Applicants therefore request that the objection and rejection of claim 2 be withdrawn.

III. Rejection under 35 U.S.C. §112, second paragraph, of claims 3 and 30

The Examiner maintained the indefiniteness rejection of claim 3 and 30 as being inconsistent with independent claim 1. The Examiner alleges that the sFv fragment recited in claims 3 and 30 is inconsistent with the limitation in independent claim 1 that the antigen binding region has a bivalent or multivalent structure.

Applicants have amended claim 1 to recite "at least one antigen binding region." Support for this amendment appears in the last paragraph of page 2 of the specification. Applicants have also amended claims 3 and 30 to change "the antigen binding region" to --at least one antigen binding region-- to be consistent with the amendment of claim 1.

Applicants submit that these amendments remove the inconsistency mentioned by the examiner in the Office Action with respect to the sFv fragment and respectfully request withdrawal of the rejection of claims 3 and 30.

IV. Rejection under 35 U.S.C. §112, first paragraph, of claim 30

The Examiner imposed a new matter rejection of claim 30, arguing that the subject matter of claim 30 is not supported by the originally filed disclosure. During the above-mentioned telephone interview on September 15, 2000, the Examiner agreed that this rejection was improper and was withdrawn. Therefore, no response to this rejection is needed.

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V. Rejections under 35 U.S.C. §103(a)

The Examiner maintained the four obviousness rejections over Bosslet et al. (*Brit. J. Cancer*, 1992) or Seemann et al. (EP 501,215) (hereinafter referred to collectively as "the primary references") in view of Huston et al. (U.S. Pat. No. 5,132,405 and *Methods in Enzymology,* 1992) (hereinafter referred to collectively as "Huston" and specifically as "Huston patent" and "Huston article"), and as necessary Bosslet et al. (EP 040,097) and Eaton et al. (EP 392,745), and further secondary references.

The Examiner's rejections appreciate that the primary references disclose a fusion protein comprising a Fab, a linker, and a human β-glucuronidase. The Examiner's rejections further appreciate that this fusion protein differs from the claimed compound by comprising a Fab (composed of H and C chains) instead of comprising an "antigen binding region . . . composed of a single polypeptide chain," *e.g.,* a sFv. The Examiner's rejections rely on Huston for teaching this element of the claims.

The Examiner has considered Applicants' previous arguments in response to these rejections, but has not been persuaded. The Examiner's position is that sFv and Fab constructs are known to be functional equivalents in the art of immunochemistry, as evidenced by the example in the Huston patent in col. 19, as well as the Huston article on page 48. The Examiner also states that Applicants' arguments concerning lack of predictability and stability are not persuasive in view of Huston's overall teaching of sFv's binding properties and increased stability. The Examiner particularly points to the Huston article's teachings on pages 68 (lines 1-5) and 87. Additionally, The Examiner is unconvinced that a person of ordinary skill in the art would not have expected an sFv and pro-drug activating enzyme fusion to result in a non-functional sFv domain. The

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Examiner cites the Huston article, pages 82-83 and 87, as well as the Huston patent's claims to a fusion construct of an sFv and an effector molecule as evidence that one of ordinary skill in the art would reasonably expect fusion proteins to work without loss of functionality or stability.

In the Advisory Action dated December 4, 2000, the Examiner clarified his position that Applicants' arguments "merely present conclusionary statements that sFv regions to tumor antigens and pro-drug activating enzymes would not have been expected to work together in a fusion protein." (*See* Advisory Action, page 2.) The Examiner further pointed to a passage in the Huston article that "suggests that some latitude exists in the design of linkers capable of producing functional sFv proteins." (*Id.* (citing Huston article, page 55, lines 4-5).)

Applicants respectfully traverse the obviousness rejections for the reasons set forth in their previous responses, incorporated herein by reference, and for the additional reasons set forth below.

A. The Prior Art Must Be Evaluated as a Whole, including Recognizing Teachings Away from the Claimed Invention

Applicants have previously addressed the fact that Huston's linker technology would not have been expected to work for a prodrug-activating enzyme at the time of the claimed invention because of the unpredictability of linker technology described in Huston. (*See* Amendment and Response dated May 11, 2000, pages 21-23; Amendment After Final dated November 7, 2000, pages 8-10.) The Examiner's position is that Huston's general statements regarding linkers can be extrapolated to a wide range of fusion proteins with a reasonable degree of success. Applicants herein

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provide copies of three documents to demonstrate the difficulty in preparing linkers in fusion protein constructs. These documents are evidence that, at the time of the claimed invention, the skilled artisan would have appreciated the difficulties associated with preparing linkers in fusion protein constructs and, therefore, would not have expected to be able to prepare a fusion protein between a prodrug-activating enzyme and an antigen binding region from Huston's general teachings.

For example, Fremont et al.'s article "Biophysical studies of T-cell Receptors and their Ligands," Current Opinion in Immunology, 8, pp. 93-100 (1996) (hereafter "Fremont") provides a review of procedures to prepare soluble T-cell receptor fragments in which the problems in preparing fusion proteins and single-chain molecules are described on pages 2-3. Furthermore, in Table 1 on pages 5-6, Fremont references several procedures where amino acid linkers were necessary to the construction of the molecule.

Perham's "Domains, Motifs, and Linkers in 2-Oxo Acid Dehydrogenase Multienzyme Complexes," Biochemistry, 30:35, pp. 8501-12 (1991) (hereafter "Perham") describes certain multienzyme complexes and on page 8507 (bottom of right column) refers to the conformational considerations in designing a synthetic peptide molecule. This passage shows the importance of flexibility of synthetic peptides. The last paragraph on page 8510 of Perham further indicates the difficulties associated with linker designs.

Finally, an excerpt from an internet chat room about linker peptides is enclosed. This excerpt is dated July 1993 and is evidence of the difficulty in designing a linker

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sequence between two independently folded proteins to avoid unwanted aggregation or steric hindrance.

Obviousness must be evaluated from the objective perspective of one actually skilled and working in the art at the time the invention was made. *See Ryko Mfg. Co. v. Nu-Star Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). To that extent, the process of determining a level of skill can assist in preventing a hindsight determination of obviousness. Evaluating what would have been obvious requires ascertaining what would have been obvious to the ordinary skilled person. *Environmental Designs v. Union Oil Co.,* 713 F.2d 693, 697, 218 U.S.P.Q. 865, 868-69 (Fed. Cir. 1983). Furthermore, the prior art must be considered as a whole without ignoring portions of the reference that lead away from obviousness. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F.2d 443, 448-49 (Fed. Cir. 1986).

In this case, the Examiner must consider the totality of the prior art and, particularly, cannot ignore the teachings of Huston and the articles cited above as to the difficulties in preparing a linker sequence. While Applicants recognize Huston's statements quoted by the Examiner that "some latitude exists in the design of linkers capable of producing functional sFv proeins," and that "[l]inker fusion between V domains need not, in principle, compromise the fidelity of an sFv binding site" (page 55, emphasis added), Applicants respectfully submit that in practice, linker design is not a simple matter of routine experimentation, as evidenced by the articles cited above, which show the difficulties encountered in designing peptide linkers.

Furthermore, even Huston recognizes that the linkers between V domains within an sFv analog, which is the topic being discussed on page 55 of the article, is very

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different from the linkers fusing an effector molecule to an sFv, which have "the potential to sterically hinder the antigen binding site." (page 57.) However, Huston does not provide specific guidance as to which linkers would be expected to work for various fusion partners or how one of ordinary skill in the art would go about selecting such linkers. Accordingly, Applicants respectfully submit that a person of ordinary skill in the art would not have extrapolated the teachings of Huston to the design of a fusion protein containing a prodrug-activating enzyme.

Thus, for these additional reasons, Applicants respectfully submit that a person of ordinary skill in the art at the time of the claimed invention would not have understood the teachings of Huston to be applied to prodrug-activating enzymes of Bosslet or Seemann with a reasonable expectation of success. Additionally, the secondary references do not cure the deficiency in the primary references, particularly Huston.

VI. Conclusion

Applicants respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1-13 and 25-33 in condition for allowance. Applicants submit that the proposed amendments of claims 1, 2, 3, 29, and 30 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

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Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: January 5, 2001

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